REMARKS

The undersigned hereby states that a computer readable form copy (CRF copy) of the substitute sequence listing and a paper copy of the substitute sequence listing, submitted in accordance with 37 C.F.R. § 1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the substitute sequence listing into the above-captioned case is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **312762002600**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: September 22, 2003

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REMARKS

Claims 1-21 are pending and stand rejected. Reconsideration of the present application is respectfully requested.

Restriction Requirement

Applicants acknowledge and confirm the oral election of restriction Group I, comprising claims 1-8. Claims 9-21 have been withdrawn.

Sequence Listing

The specification has been amended to include sequence identification numbers for sequences disclosed in Figures 6a-c and in Examples 1 and 7 mentioned by the Examiner in the Office Action dated May 20, 2003. With respect to the polypeptide HASS, the corresponding amino acid sequence is included in the substitute sequence listing as SEQ ID NO:7.

A paper and electronic copies of the sequence listing accompany this Amendment and Response. The undersigned hereby states that a computer readable form copy (CRF copy) of the substitute sequence listing and a paper copy of the substitute sequence listing, submitted in accordance with 37 C.F.R. § 1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the substitute sequence listing into the above-captioned case is respectfully requested.

Applicants were in possession of the claimed invention at the time the application was filed

Claims 1-8 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to be supported by the specification in such a way as to reasonably convey to a skilled artisan that the inventors were in possession of the claimed invention at the time the application was filed. To satisfy the written description requirement a patent application must describe the invention in sufficient detail that one of skill in the relevant art could reasonably conclude that the inventor was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991). Applicants need not precisely recite each and every element of a claim limitation in the specification in order to satisfy the written

description requirement. *See Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000). Moreover, "[a] patent need not teach, and preferably omits, what is well know in the art." *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), *cert. denied*, 484 U.S. 954 (1987).

SAHH

The Examiner noted that claims 1-6, which are directed to a method of assessing the level of SAM in a biological fluid, utilize three independent enzymatic activities. The enzymes recited in these claims include glycine N-methyltransferase (GMT), S-adenosylhomocysteine hydrolase (SAHH) or a recombinant for of SAHH with a histidine tag located at the N-terminus of the protein (His•SAHH), and homocysteinase (HCYase).

The Examiner alleged in the Office Action that the specification only provided a single form of SAHH and that no structure/function relation for the enzyme was provided. Applicants respectfully disagree.

As a preliminary matter, Applicants submit that the structure of SAHH is provided in the specification, specifically in the form of nucleic acid and amino acid sequences. This structural information for the disclosed species of SAHH enzyme coupled with disclosed function of the enzyme, that is, the ability to catalyze the conversion of S-adenosyl homocysteine to homocysteine, is sufficient structural and functional information to allow one of ordinary skill in the art to reasonably conclude that Applicants were in possession of the claimed invention at the time it was filed. Furthermore, the present specification discusses SAHH isolated from a number different organisms. For example, a detailed discussion of the SAHH enzyme is provided in the Background section of the specification. The Enzyme Commission number for the class of enzymes is provided (Page 2, lines 1-2). The specification notes that the enzyme was initially cloned from *Trichomonas vaginalis* and has been characterized (Page 2, lines 6-7). Other sources of the SAHH enzyme are also discussed in the specification. For example, the enzyme

from rat liver, other animal sources, and a plant source are all disclosed (Page 2, line 19 to page 3, line 2).

Applicants submit that the present specification contains disclosure regarding a number of forms of SAHH and that a structure/function relationship is provided. As such, there is sufficient disclosure in the specification to allow one of ordinary skill in the art to reasonably conclude that Applicants were in possession of a number of forms SAHH at the time the application was filed.

Glycine N-Methyltransferase (GMT) and Homocysteinase (HCY)

The specification allegedly failed to provide teachings regarding the source of glycine N-methyltransferase (GMT) or homocysteinase (HCYase) activities, *i.e.*, a commercial or biological source. Each of these enzymes is commercially available from AntiCancer, Inc. (San Diego, CA). Additionally, methodologies for preparing these enzymes were notoriously well known in the art at the time the application was filed. For example, recombinant expression and purification of GMT and HCYase was reported in the literature before the filing date of the present application (Ogawa, et al., "Recombinant expression of rat glycine N-methyltransferase and evidence for contribution of N-terminal acetylation to co-operative binding of S-adenosylmethionine." Biochem J. 327(Pt 2):407-12 (1997) and Han et al., "High expression, purification and properties of recombinant homocysteine, α, γ-lyase." Protein Expression and Purification 14, 267-274, 1998). In light of the teachings present in the art regarding these enzymes and their commercial availability, Applicants submit that their recitation in the claims is adequately supported in the specification.

Possession of the invention

Upon reading the present specification, one of ordinary skill in the art would reasonably conclude that Applicants were in possession of the claimed invention at the time the present

application was filed. The skilled artisan would come to this conclusion, in part, because of the detailed guidance provided in the specification coupled with knowledge of the art.

As noted in the specification S-adenosylmethionine (SAM) is converted to S-adenosyl homocysteine (SAH) by glycine methyltransferase (GMT)(Pathway shown on Page 6). An assay for determining glycine N-methyltransferase activity was well known in the relevant art at the time the present application was filed (*for example*, *see* Cook & Wagner, "Glycine N-methyltransferase is a folate binding protein of rat liver cytosol." Proc. Natl. Acad. Sci. USA 81:3631-3634, 1984). Thus, a skilled artisan would know how to use GMT to catalyze the conversion of SAM to SAH.

The specification also teaches that S-adenosyl homocysteine (SAH) is metabolized to homocysteine by SAH hydrolase (SAHH)(Pathway shown on Page 6). An assay for determining SAHH activity in catalyzing the formation of either HC or SAH was well known in the relevant art at the time the present application was filed (*for example*, *see* Richards, *et al.*, "Adenosylhomocysteine Hydrolase: Crystallization of the Purified Enzyme and its Properties." J. Biol. Chem. 253:4476-4480, 1978). Thus, a skilled artisan would know how to use SAHH to catalyze the conversion of SAH to HC or HC to SAH.

Homocysteine (HC) is also taught in the specification as being metabolized into alpha-ketoglutarate, hydrogen sulfide (H_2S), and ammonia (NH_3) by homocysteinase (Pathway shown on Page 6). The assay described in Example 6 measures the amount of H_2S generated by the metabolism of HC using the dialkyl phenylene diamine reagent *N,N*-Dibutylphenylenediamine (DBPDA). The amount of H_2S generated correlates to the amount of HC in the sample.

As discussed in the specification, determination of SAM levels in a sample may be accomplished by measuring one or more reaction products in the sample, where the amount of the reaction product or products is directly proportional to the SAM levels in the sample (Page 3, lines 14-24). Example 6 provides a recipe and directions that a skilled artisan could easily use to practice the claimed invention. As discussed in the specification, the concentration of H_2S

produced in the assay correlates to the amount of SAM starting material. (Page 3, lines 14-24). The guidance provided in the specification generally, in Example 6, and the knowledge in the art, allows the skilled artisan to convert the SAM in a sample to hydrogen sulfide (H_2S), which can then be quantified. Thus, one of ordinary skill in the art could calculate the amount of SAM in the starting material.

In light of the discussion above, Applicants submit that one of ordinary skill in the art would have reasonably concluded, upon reading the specification in view of the knowledge of the art, that Applicants were in possession of the claimed invention at the time the application was filed. As such, Applicants respectfully submit that the present rejection be withdrawn.

The claimed subject matter is recited distinctly and with particularity

Claims 1-8 stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. The specific rejections are discussed below.

Claims 1, 7, and 8 were rejected for containing the undefined abbreviation "His•SAHH". Claims 1, 7, and 8 have been amended to define the abbreviation recited in the claims. For example, the claims were amended to define "His•SAHH" as a "(N-terminal histidine tagged SAHH)". Support for this amendment is found throughout the specification, specifically at page 5, lines 14-16. In view of these amendments, Applicants request that the present rejection be withdrawn.

Claim 8 was also rejected as being indefinite for allegedly failing to particularly pointing out and distinctly claiming the subject matter Applicants regard as the invention. It was not clear to the Examiner whether the claim was directed to a method for determining the amount of SAM or an assay composition. Applicants have amended the preamble of claim 8 to recite "[a] method of determining SAM concentration". Applicants submit that this amendment serves to more clearly define the subject matter Applicants regard as the invention. As such, Applicants request that the present rejection be withdrawn.

Additionally, the pending claims have been amended to recite relative amounts of the various enzymes called for in the claimed methods. Support for these amendments can be found in provisional application 60/176,444, which is the parent of the present case. These amendments serve to further clarify the subject matter Applicants regard as the invention.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **312762002600**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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